RENAL MANAGEMENT AND DOSE ADJUSTMENT ADVICE FOR HEALTHCARE PROFESSIONALS WITH ADULT PATIENTS RECEIVING TENOFOVIR DISOPROXIL FUMARATE (TDF)[1]

Important Points to Consider

- ✓ Check all patients' creatinine clearance before starting TDF therapy
- ✓ During TDF therapy, renal function (creatinine clearance and serum phosphate) should be assessed regularly (every 4 weeks during the 1st year and then every 3 months) (see Table 1 below)
- ✓ Consider more frequent monitoring of renal function in patients at risk for renal impairment
- ✓ In patients with renal impairment, TDF should only be used if the potential benefits of treatment outweigh the potential risks, and the dosing interval of TDF may need to be prolonged (see Table 2 overleaf)
- ✓ Consider interrupting treatment with TDF in patients with creatinine clearance decreased to <50 mL/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L)
- ✓ Avoid concurrent or recent use of nephrotoxic medicinal products

TDF renal safety profile in chronic hepatitis B (CHB) studies

In studies of patients with compensated CHB, ≤1.5% of patients who received TDF throughout 288 weeks had a confirmed renal event (≥0.5 mg/dL increase in serum creatinine, serum phosphate <2 mg/dL, or creatinine clearance <50 mL/min).[2]

Post-marketing safety surveillance (all indications)

Rare events of renal failure, renal impairment and proximal tubulopathy (including Fanconi syndrome) have been reported. In some patients proximal renal tubulopathy has been associated with myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscle weakness, hypokalaemia and hypophosphataemia.[1]

Monitoring of renal function

The recommendations for monitoring renal function in all patients prior to and during TDF therapy are provided in Table 1 below.

Table 1: Monitoring of renal function[1]

	Prior to TDF	During 1st year on TDF*	>1 year on TDF*
Frequency	At baseline	Every 4 weeks	Every 3 months
Parameter	Creatinine clearance	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate

* In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Use of TDF should be avoided with concurrent or recent use of a nephrotoxic medicinal product and drugs secreted by the same pathway; if concomitant use is unavoidable, renal function must be monitored weekly.[1]

If serum phosphate is <1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to <50 mL/min in any patient receiving TDF, renal function should be re-evaluated within 1 week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with TDF in patients with creatinine clearance decreased to <50 mL/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L).[1]

Use in Renal Impairment

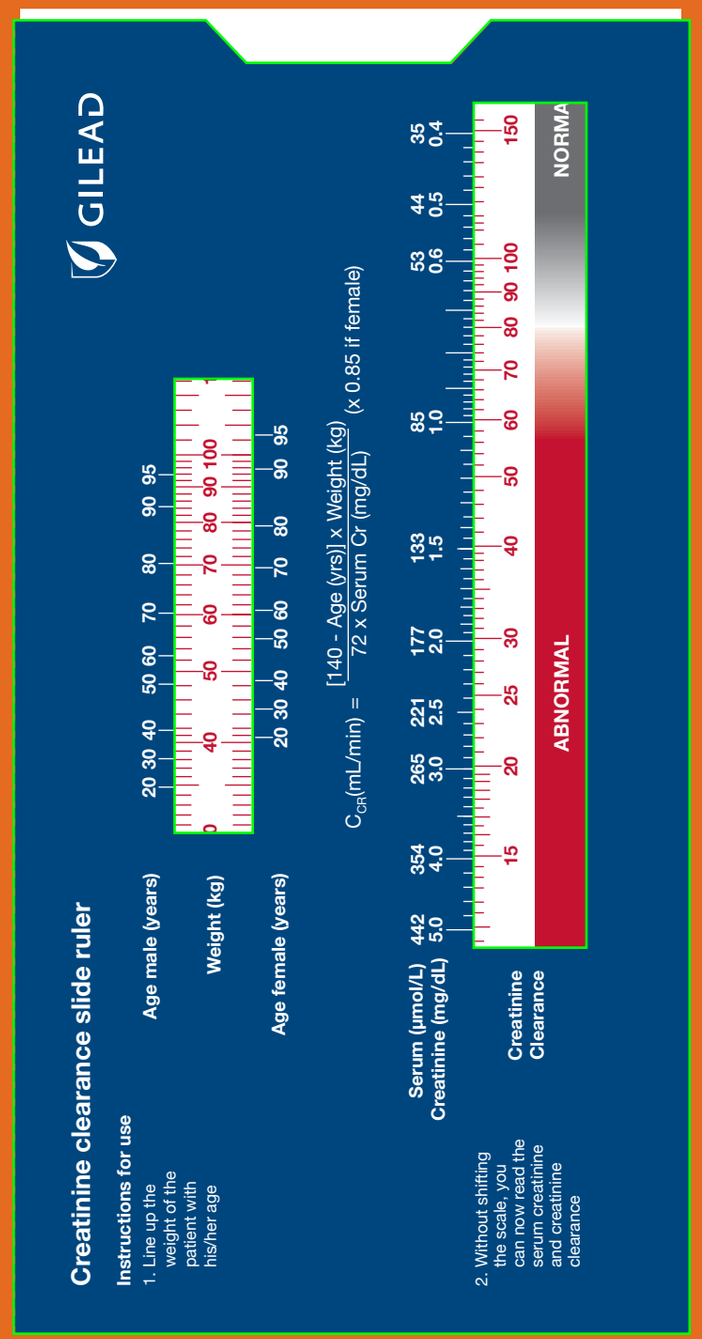
In patients with renal impairment, TDF should only be used if the potential benefits of treatment outweigh the potential risks, and close monitoring of renal function is recommended. TDF is principally eliminated via the kidney and exposure to tenofovir increases in patients with renal dysfunction. Limited data from clinical studies support once daily dosing of TDF in patients with mild renal impairment (creatinine clearance 50–80 mL/min). The dosing interval adjustment guidelines for patients with creatinine clearance <50 mL/min are shown in Table 2 below.

Table 2: Dosing interval adjustments for patients with renal impairment[1]

	Creatinine clearance (mL/min)			Haemodialysis patients
	50–80	30–49	10–29	
Recommended TDF dosing interval	Every 24 hours (no adjustment required)	Every 48 hours*	Not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) or in haemodialysis patients. If no alternative treatment is available, prolonged dose intervals may be used: Severe renal impairment – every 72–96 hours (dosing twice a week). Haemodialysis patients – every 7 days following completion of a haemodialysis session.**	

* Dose interval adjustment is recommended for patients with creatinine clearance between 30 and 49 mL/min. This dose interval adjustment has not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients. Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response.

** Assuming 3 haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis. No dosing recommendations can be given for non-haemodialysis patients receiving TDF with creatinine clearance <10 mL/min.[1]



VIREAD® PRESCRIBING INFORMATION

Presentation: Viread film-coated tablet containing 245mg of tenofovir disoproxil (as fumarate), equivalent to 300mg of tenofovir disoproxil fumarate, or 136mg of tenofovir.
Indications: 1) The treatment of chronic hepatitis B (CHB), in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. 2) treatment of CHB in adults with decompensated liver disease. 3) In combination with other antiretroviral medicinal products for treatment of HIV-1 Infected adults aged 18 years and over.
Dosage & Administration: Adults: One tablet (245mg) once daily taken with food. Children and adolescents: not recommended. Elderly: Insufficient data are available on which to make dose recommendations for patients over the age of 65 years – caution should be exercised. Not recommended in patients with severe renal impairment (creatinine clearance (CrCl) <30ml/min). No dose modification necessary in patients with mild to moderate liver disease. Optimal duration of treatment is unknown.
Contraindications: Known hypersensitivity to tenofovir, tenofovir disoproxil fumarate, or any of the excipients.
Warnings and Precautions: Renal: Renal failure and impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice. It is recommended that CrCl is calculated in all patients prior to therapy initiation and renal function monitored every 4 weeks for the first year and every 3 months thereafter. In patients at risk of renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function. Tenofovir disoproxil fumarate should only be used in these patients if the potential benefits outweigh the risks. For patients with CrCl < 50ml/min, the dosing interval should be adjusted. Adults: moderate renal impairment (CrCl 30-49 ml/min) – 1 tablet every 48 hours. Severe renal impairment (CrCl < 30 ml/min) and in patients who require haemodialysis use of tenofovir disoproxil fumarate is not recommended. Refer to SPC for full monitoring and dose adjustment recommendations.
HIV Co-infection: HIV antibody testing should be offered to all HBV-infected patients before initiating tenofovir disoproxil fumarate therapy. Due to the risk of development of HIV resistance, tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients. Patients must be advised tenofovir disoproxil has not been proven to prevent the risk of transmission of HIV or HBV to others through sexual contact or contamination with blood and appropriate precautions must be used.
Exacerbations of hepatitis: Flares on treatment: Spontaneous exacerbations in CHB are relatively common. Patients with cirrhosis may be at higher risk for hepatic exacerbations and therefore should be monitored closely. However it also should be noted that increase in ALT can be part of HBV clearance during therapy with tenofovir. Flares after treatment discontinuation: Acute exacerbations of hepatitis have also been reported in patients who have discontinued hepatitis B therapy. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of therapy. Treatment discontinuation is not recommended in patients with advanced liver disease or cirrhosis, since post-treatment exacerbations of hepatitis may lead to hepatic decompensation. Co-infection with hepatitis C or D: There are no data on the efficacy of tenofovir in patients co-infected with hepatitis C or D virus. Hepatic decompensation: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

References
1. VIREAD Summary of Product Characteristics
2. Marcellin P *et al.* AASLD 2012, Poster 374

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Hepatic disease: Safety and efficacy data are very limited in liver transplant patients. Other: Lactic acidosis and lipodystrophy – refer to SPC for recommendations regarding monitoring. Viread may cause a reduction in BMD. Bone abnormalities (may be associated with proximal renal tubulopathy). Triple nucleoside/nucleotide therapy. Mitochondrial dysfunction. Immune Reactivation Syndrome. Osteonecrosis. Avoid in antiretroviral experienced patients harbouring K65R mutation.
Interactions: Low potential for CYP450 mediated interactions with other medicinal products. Viread should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate or adefovir dipivoxil, nephrotoxic agents or medicinal products that reduce renal function or compete for active tubular secretion. Monitor renal function if tenofovir disoproxil fumarate administered with tacrolimus. Co-administration with didanosine is not recommended as it may result in a 40-60% increase in systemic exposure to didanosine which may increase the risk of didanosine-related adverse events. Co-administration with 400 mg daily didanosine has been associated with significant decreases in CD4 cell counts. A reduced dose of 250 mg didanosine administered with tenofovir disoproxil fumarate has been associated with reports of high rates of virological failure. Co-administration with lopinavir/ritonavir; 30% increase in tenofovir AUC. Co-administration with atazanavir/ritonavir decreased atazanavir concentrations, but increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir associated adverse events including renal disorders. Food has been shown to enhance the bioavailability of Viread. Refer to SPC for drug interaction details for protease inhibitors, NRTIs, NNRTIs.
Use in pregnancy and lactation: The use of Viread may be considered during pregnancy. Viread should not be used during breast feeding.
Side effects: Very commonly reported adverse events (≥1/10): hypophosphataemia*, dizziness, diarrhoea, vomiting, nausea, rash, asthenia. Common (≥1/100 to <1/10): flatulence, headache, abdominal pain, abdominal distension, fatigue, increased transaminases. Uncommon (≥ 1/1,000 to < 1/100): hypokalaemia*, pancreatitis, rhabdomyolysis*, muscular weakness, increased creatinine. Rare (≥1/10,000, <1/1,000): lactic acidosis, hepatic steatosis, hepatitis, angioedema, osteomalacia*, myopathy*, renal failure, acute renal failure, proximal renal tubulopathy including Fanconi syndrome, acute tubular necrosis, nephritis, nephrogenic diabetes insipidus. The side effects marked * may occur as a consequence of proximal renal tubulopathy. In patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART), cases of osteonecrosis have been reported. Inflammatory reaction to asymptomatic or residual opportunistic infections may arise in patients with severe immunodeficiency at the time of initiation of CART. CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia and lipodystrophy. In patients with CHB, exacerbations of hepatitis during treatment may arise. Refer to SPC for full information on adverse events.
Overdosage: If overdose occurs, monitor for evidence of toxicity. Apply standard supportive treatment if necessary. Tenofovir can be removed by haemodialysis.
Pharmaceutical Precautions: No special precautions for storage or handling.
Legal Category: Prescription only medicine
Package Quantities: Bottle of 30 film coated tablets
Marketing Authorisation numbers: EU/1/01/200/001
Further information is available from the marketing authorisation holder: Gilead Sciences International Ltd, Granta Park, Abington, Cambridge CB21 6GT.
Telephone: + 44 (0) 208 587 2394. Email: intlmed.info@gilead.com
CONSULT THE SUMMARY OF PRODUCT CHARACTERISTICS BEFORE PRESCRIBING PARTICULARLY IN RELATION TO SIDE EFFECTS, PRECAUTIONS AND CONTRAINDICATIONS.
Viread is a registered trademark
Date of PI preparation: August 2011.

Suspected adverse drug reactions (ADRs) should be reported to the Medicines Authority Post-Licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA or at http:/www.medicinesauthority.gov.mt/pub/adr.doc

Suspected adverse drug reactions may also be reported to GILEAD SCIENCES INTERNATIONAL LTD via email to csafety@gilead.com or tel: +44 (0) 1223 897500 or to AM MANGION Ltd via email to pv@ammangion.com.mt or tel: (+356) 2397 6333

GILEAD

Renal monitoring tool

Prescribing information can be found on the back once unfolded.